De novo formation of the biliary system by TGFbeta-mediated hepatocyte transdifferentiation.

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Public Summary:
Our study shows that hepatocytes can become cholangiocytes and form a functional biliary system in mice that are born without the biliary system. This ability is remarkable because hepatocytes are responsible for providing the liver's synthetic and metabolic functions, including producing bile, whereas the main function of cholangiocytes is to form tubes that transport bile out of the liver into the intestine. Viewed together with recent findings that cholangiocytes can become hepatocytes if their ability to regenerate themselves is impaired, as in chronic liver diseases, our study suggests conversion of hepatocytes into cholangiocytes and vice versa as the main backup mechanism for liver regeneration. This mechanism could be harnessed for therapy of liver diseases in which cholangiocytes or hepatocytes are lacking or functionally impaired.

Scientific Abstract:
Transdifferentiation is a complete and stable change in cell identity that serves as an alternative to stem-cell-mediated organ regeneration. In adult mammals, findings of transdifferentiation have been limited to the replenishment of cells lost from preexisting structures, in the presence of a fully developed scaffold and niche(1). Here we show that transdifferentiation of hepatocytes in the mouse liver can build a structure that failed to form in development-the biliary system in a mouse model that mimics the hepatic phenotype of human Alagille syndrome (ALGS)(2). In these mice, hepatocytes convert into mature cholangiocytes and form bile ducts that are effective in draining bile and persist after the cholestatic liver injury is reversed, consistent with transdifferentiation. These findings redefine hepatocyte plasticity, which appeared to be limited to metaplasia, that is, incomplete and transient biliary differentiation as an adaptation to cell injury, based on previous studies in mice with a fully developed biliary system(3-6). In contrast to bile duct development(7-9), we show that de novo bile duct formation by hepatocyte transdifferentiation is independent of NOTCH signalling. We identify TGFbeta signalling as the driver of this compensatory mechanism and show that it is active in some patients with ALGS. Furthermore, we show that TGFbeta signalling can be targeted to enhance the formation of the biliary system from hepatocytes, and that the transdifferentiation-inducing signals and remodelling capacity of the bile-duct-deficient liver can be harnessed with transplanted hepatocytes. Our results define the regenerative potential of mammalian transdifferentiation and reveal opportunities for the treatment of ALGS and other cholestatic liver diseases.